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LARSON & TAYLOR, PLC
1199 NORTH FAIRFAX STREET
SUITE 900
ALEXANDRIA, VA 22314

EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/380,327	Applicant(s) ROBERTSON ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-62,64-71,73,75-77,79,81 and 83-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-62,64-71,73,75-77,79,81 and 83-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 50-62, 64-71, 73, 75-77, 79, 81, and 83-93 are pending.

2. Upon reconsideration, Claims 83 drawn to the method of including the administration of plasmin to increase the level of active TGFβ in the method of eliciting an immune reaction in prospective mammalian mother to one or more antigens of a prospective father to alleviate symptoms of an infertility condition comprising exposing said prospective mother to said one or more antigens of prospective father and substantially purified TGFβ leading to tolerance to said one or more antigens and claim 92 drawn to the step of diagnosing or testing whether the male has adequate levels of TGFβ or the female of has the capactity to activate TGFβ or alternatively whether anti-sperm antibodies exist before exposing said prospective mother to said one or more antigens of prospective father and substantially purified TGFβ leading to tolerance to said one or more antigens are hereby rejoined with Group XII (now claims 60-62, 64-71, 73, 75-77, 79, 81 and 93-93). Therefore, the requirement of Group XII (now claims 60-62, 64-71, 73, 75-77, 79, 81 and 93-93) and Groups I-XI and XIII-XLII is still deemed proper and is therefore made FINAL.

3. In view of the amendment filed 6/18/01, the following rejections remain.

4. The drawings, filed on 9/3/99, stand not in compliance with 37CFR 1.84(a). Please see attached PTO 948 mailed 3/14/01. Appropriate correction is required. It is noted that formal drawings will be submitted at a later time prior to or at payment of the issue fee.

5. The disclosure is objected to because the abstract filed on 6/18/01 is not on a separate sheet as required by 37 CFR 1.72(b).

6. The following new grounds of rejection are necessitated by the amendment filed 6/18/01.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 50-62, 64-71, 73, 75-77, 79, 81, and 83-93 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliciting an immune reaction in a prospective mammalian mother to sperm antigens of a prospective father to alleviate symptoms of an infertility condition, said method comprising administering said prospective mother to said sperm antigens of said prospective father and to substantially purified TGFβ, said method leading to tolerance to said sperm antigens and alleviation of said infertility condition, **does not** reasonably provide enablement for a method of eliciting *any* immune reaction in a prospective mammalian mother using (1) *any* one or more antigens, (2) *any* antigen on either the sperm or on the conceptus, (3) *any* MHC antigens, (4) *any* TGFβ is modified, (5) *any* TGFβ wherein the modification comprises substitution, deletion, or addition mutants, (6) *any* peptide fragments of TGFβ, and (7) *any* derivative or analog thereof leading to tolerance to any antigens and alleviation of said infertility condition.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only a method of eliciting an immune response in a prospective mother to sperm antigens (antigens on the sperm) and MHC class I by co administering sperm antigens in the form of the prospective father's ejaculate and TGFβ together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGFβ after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions.

The specification does not teach how to make and use *any* antigen for a method of induction of tolerance that leads to alleviation of infertility condition because applicants have not identified all potential antigens other than the MHC class I antigen on the sperm from the prospective father for induction of tolerance in the prospective mother. The state of the art does not recognize MHC class II antigen play a important role in impaired reproductive functions associated with infertility such as miscarriage, spontaneous abortion, or pre-eclampsia. Given the indefinite number of undisclosed antigens, it is unpredictable which undisclosed antigen of the

prospective father would be useful for induction of tolerance, in turn, for a method of alleviating the symptoms of infertility condition.

Further, there is no guidance and working example as to which amino acid within the full length sequence of TGFβ can be deleted and whether the "fragment" of any TGFβ after deletion would maintain the structure and would have similar function as TGFβ for a method of inducing tolerance in a prospective mother to one or more antigens of a prospective father to alleviate symptoms of infertility. There is no guidance in the specification as to what type and number of amino acids within the TGFβ can be added or substituted and whether after addition or substitution would retain both structure and biological activity. The state of the art is that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable for analogs (See Ngo et al, of record, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Furthermore, the specification does not reasonably provide enablement for any "effective derivative or analogs thereof" other than TGFβ1. Although the function of TGFβs appear to be overlapping and converging on the TGFβ receptor and the signaling transduction factors SMAD2 or SMAD3, the state of the prior art is such that the functions of TGFβ1, TGFβ2, TGFβ3 and analogs thereof including activin and inhibin are distinct and largely nonoverlapping based on targeted disruption of the three TGFβ genes (See Dunker et al, of record, Eur J Biochem 267(24): 6982-8). Further, the specification as filed discloses that "the specificity of TGFβ to be co-administered with the male antigens is at present not entirely clear, and because TGFβ1 is thought to be responsible whereas TGFβ2, TGFβ3 are less important, it is more likely that TGFβ1 is to be used" (See page 9, line 7-9). Given the indefinite number of undisclosed modified TGFβ, analog and fragment thereof, it is unpredictable which undisclosed modified TGFβ would have the same function and structure as the TGFβ1.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 6/14/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) applicants have deleted reference in the claims to "derivatives and analogs of TGF", (2) applicants maintain the reference to isotype of TGF, which

because of their closely related structure to TGFβ1, are fully expected to be useful and to work in the present invention.

However, claim 90 still recites TGFβ or derivative or analog thereof. Further, there is no guidance and working example as to which amino acid within the full length sequence of TGFβ can be added, deleted or modified and whether the modified TGFβ after addition, deletion or substitution would maintain both structure and would have similar biological function as TGFβ, in turn, would be useful for a method of inducing tolerance in a prospective mother to one or more antigens of a prospective father to alleviate symptoms of infertility. The specification as filed discloses only administering TGFβ1 and with sperm antigens to a prospective mother. There are no additional modified TGF comprises substitution, deletion or addition mutants, analog or derivative thereof.

9. Claims 50-62, 64-71, 73, 75-77, 79, 81, and 83-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses only (1) The specification discloses only a method of eliciting an immune response in a prospective mother to sperm antigens (antigens on the sperm) and MHC class I by co administering sperm antigens in the form of the prospective father's ejaculate and TGFβ together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGFβ after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions.

The specification does not reasonably provide a **written description** of a method of eliciting *any* immune reaction in a prospective mammalian mother using (1) *any* one or more antigens, (2) *any* antigen on either the sperm or on the conceptus, (3) *any* MHC antigens, (4) *any* TGFβ is modified, (5) *any* TGFβ wherein the modification comprises substitution, deletion, or addition mutants, (6) *any* peptide fragments of TGFβ, and (7) *any* derivative or analog thereof for induction of immune tolerance and alleviation of symptoms of infertility condition.

With the exception of the specific antigen and TGFβ mentioned above, there is insufficient written description about the structure associated with function of *any* antigens, *any* TGFβ is modified, *any* TGFβ wherein the modification comprises substitution, deletion, or addition mutants, *any* peptide fragments of TGFβ, and *any* derivative or analog thereof.

Given the lack of a written description of any additional species of antigen, modified TGFβ, analog and fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 56 and 65-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said TGFβ" in claim 56 has no antecedent basis in base claim 51. The base claim 51 requires a mucosal surface of the prospective mother is exposed to one or more antigen.

The recitation of "one or more antigens are administered on sperm cells of the prospective father" in claims 65 and 66 is ambiguous and indefinite. The specification discloses that the antigens are from the sperm cells, which are already located on the surface of the sperm of the prospective father. Appropriate correction is required.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 50-62, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; PTO 1449) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892).

The '825 patent teaches a method of treating infertility by administering TGFβ, such as TGFβ1, TGFβ2, TGFβ3, and TGFβ4 (See column 5, line 9-11, in particular) along with antigens such as ovum, sperm or conceptus into the reproductive track (genital mucosal surface) of the a female to increase the success rate of implantation (See column 5 line 9-12, claim 4 of '825 patent, in particular). The reference TGFβ may be administered either before, after or simultaneously with the male antigens such as the sperms of the prospective father which are known to express MHC class I molecule on the surface and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21). The reference TGFβ or analog may be administered by injection, patch, and gels that are slow release (See column 5, line 1-2; column 6, line 45-55). The '825 patent further teaches a method of diagnosing or testing the presence of active and/or immunological TGFβ in female or diagnosing mammals with infertility due to inadequate TGFβ (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The '825 patent teaches stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

The claimed invention as recited in claim 50 differs from the references only by the recitation that the method eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition.

The claimed invention as recited in claims 61-62 differs from the references only by the recitation that the antigen is an MHC class I antigen of the prospective father.

The claimed invention as recited in claim 66 differs from the references only by the recitation that the one or more antigens are presented in purified or semi-purified form.

The claimed invention as recited in claim 67 differs from the references only by the recitation that the method include inert or adjuvant carriers.

Clark *et al* teach bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Chaouat *et al* teach immunizing female with the male leukocyte purified from spleen which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular). Chaouat *et al* teach the protection is associated with active suppression against maternal cell-mediated immunity (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of administering TGFβ, such as TGFβ1, TGFβ2, TGFβ3, and TGFβ4 (See column 5, line 9-11, in particular) along with antigens such as ovum, sperm or conceptus as taught by the '825 patent with the method of immunizing female with paternal leukocyte antigen as taught by Chaouat *et al* and Feinberg *et al* for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by the '825 patent, Clark *et al,* Chaouat *et al* and Feinberg *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '825 patent teaches stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular). Chaouat *et al* teach immunizing female with the male leukocyte which carried the paternal MHC class I haplotype can lead to protection of fetus from maternal cell-mediated immunity (See Abstract, in particular). Clark *et al* teach bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular). Claims 55-56 are included in this rejection because the recitation of administering TGFβ and one or more antigens

are systemically or each administered at a first site and a different site is an obvious variation of the teaching of the '825 patent since the '825 patent teaches TGFβ can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made. Claims 79 and 80 are included in this rejection because the recitation of active form is within the teachings of '825 patent because administering TGFβ and antigens lead to increase the success rate of implantation, which is the active form of TGFβ (See entire document, Claims of 825 patent, in particular). Claim 86 is included in this rejection because the recitation of multiple exposure to TGFβ and male antigen is within the purview of one of ordinary skilled in the art based on the teachings of the '825 patent.

15. Claims 66-67 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-65, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 and further in view of Harlow *et al* (in A Laboratory Manual, Cold Spring Harbor Laboatory, page 61, 1988; PTO 892), World Health Organization (in World Health Organization Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction, Cambridge University Press, NY 1987, PTO 892) and Martin-Villa *et al* (Biol Reprod 55(3): 620-9, Sept 1996; PTO 892).

The teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claims 66-67 differs from the references only by the recitation that one or more antigens are presented in purified or semi-purified form.

The claimed invention as recited in claim 71 differs from the references only by the recitation that the exposure of the one or more antigens is to the prospective mother's genital tract in the form of the prospective father's ejaculate, and the level of exposure is determined by the cell count and antigenic density on the surface of such cells.

Harlow *et al* teach a simple method of purifying any protein antigen by polyacrylamide gels electrophoresis (See page 61, in particular). Harlow *et al* having pure antigen provides the best case for the production of antibodies.

The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate (See page 5, page 9, Counting the spermatozoa, in particular) and various methods of determining male infertility.

Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry and relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA (See entire document, Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify antigen as taught by Harlow *et al* using the antigens from the sperm or conceptus as taught by the '285 patent or the semi-purify sperm antigens from the ejaculate by washing and counting as taught by the WHO Laboratory Manual for the Examination of Human Semen or the purified human spermatozoa from the prospective father 's ejaculate and determining the antigen density by double labeling cytofluorometry and relevant antibody as taught by Martin-Villa *et al* to determine the levels of antigen prior to exposing the prospective mother's genital tract to one or more antigens to induce immune tolerance to the antigen(s) of the prospective father for a method of eliciting an immune reaction and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow *et al* teach purifying any protein antigen by polyacrylamide gels electrophoresis is a simple method (See page 61, in particular). The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate is useful for (See page 5, page 9, Counting the spermatozoa, in particular) determining male infertility. Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry using relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA, as one of the indicator for male fertility (See entire document, Abstract, in particular).

16. Claims 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-65, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 and further in view of Tuan *et al* (Connect Tissue Res 34(1): 1-9, 1996; PTO 892) or Lyons *et al* (J Cell Biol 110(4): 1361-7, April 1990; PTO 892).

The teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 75 differs from the references only by the recitation that the TGFβ is modified.

The claimed invention as recited in claim 76 differs from the references only by the recitation that the modified TGFβ wherein the modification comprises substitution, deletion, or addition mutants or peptide fragments of TGFβ.

Tuan *et al* teach modified TGFβ and analog of TGFβ such as TGFβ1-1 and TGF-B1-F2 fusion proteins from *E coli*; the reference modified TGFβ and analog has comparable antiproliferative activity to purified platelet TGF-beta 1 (See abstract, in particular).

Lyons *et al* teach peptide fragment of TGFβ such as N terminal deletion using plasmin or acid activation and the resulting peptide fragment of TGFβ is active (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF beta as taught by the '825 patent for the modified TGFβ analog as taught by Tuan *et al* or the active fragment of TGFβ as taught by Lyons *et al* for a method of eliciting an immune reaction in a prospective mammalian mother by exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Tuan *et al* teach modified TGFβ and analog of TGFβ has comparable antiproliferative activity to purified platelet TGF-beta 1 (See abstract, in particular). Lyons *et al* teach peptide fragment of TGFβ such as active TGFβ by N terminal deletion can be activated by plasmin or acid activation (See abstract, in particular).

17. Claims 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-67, 70, 73, 77, 79, 81, 89, 90, 92 and 93 and further in view of Grainger *et al* (Nat Med 1(9): 932-7, Sep1995; PTO 892).

The teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 83 differs from the references only by the recitation that the method of treating includes administration of plasmin as to increase the level of active TGFβ.

The claimed invention as recited in claim 84 differs from the references only by the recitation that the TGFβ is administered in an unpurified form using a biological source rich in TGFβ.

The claimed invention as recited in claim 85 differs from the references only by the recitation that the TGFβ is administered in the form of platelets.

Grainger *et al* teach transforming growth factor beta 1 (TGF-beta 1) is a platelet-derived cytokine and human whole platelets is a rich source of inactive TGF-beta 1, which can be activate by plasmin (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the active TGF beta as taught by the '825 patent for the unpurified form using a biological source rich in TGFβ such as the platelets along with plasmin to activate the inactive form of TGFβ as taught by Grainger *et al* for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Grainger *et al* teach platelet is a rich of inactive TGFβ and which can be activate by plasmin (See abstract, in particular).

18. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-67, 70, 73, 77, 79, 81, 89, 90, 92 and 93 and further in view of Heidenreich *et al* (Am J Reprod Immunol 31(2-3): 69-76, Mar-Apr 1994; PTO 892).

The teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 92 differs from the references only by the recitation that the method includes testing whether anti-sperm antibodies exist.

Heidenreich *et al* teach a method of detecting anti-sperm antibody in infertile male using a highly sensitive and reproducible ELISA assay (See abstract, in particular). The reference assay synchron ELISA (Synelisa) is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the step of diagnosing whether anti-sperm antibodies exist using the assay as taught by Heidenreich *et al* with the method of treating infertility by administering TGFβ and male antigens as taught by the '825 patent, Clark *et al,* and Chaouat *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Heidenreich *et al* teach anti-sperm antibody is associated with male infertility and the reference assay is useful for is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

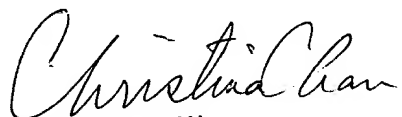
19. Claims 68-69, 87-88 and 91 are free of art.

20. No claim is allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
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